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THE RATE OF GROWTH FOLLOWING AN INITIAL PERIOD OF SUPPRESSION[1]

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The present paper attempts to discuss quantitative aspects of the growth of animals which, though eventually reaching the same approximate size, reached that size at widely different ages. The data upon which the discussion rests have been drawn from the published articles of several workers in the field of animal physiology and deal with the growth, under varying conditions, of the albino rat.

When the growth of an animal is suppressed for a long time the capacity to grow persists, even beyond the period at which growth ordinarily ceases in that species. The studies of Osborne and Mendel have amply demonstrated the existence of this capacity to grow and to reach the weight characteristic of mature individuals of their species. The growth impulse is something inherent in the organism. The environment, while modifying the amount of growth, has less influence upon the specific character of the growth of organisms than has the essential constitution of the living substance. A quantitative study of the growth rate of organisms ought, therefore, to lead to considerations of a fundamental nature.

The nature of the growth rate in general is revealed by the use of a few simple equations of the first order. They show that growth proceeds at a rate similar to that of a monomolecular reaction. Robertson[2] and others have discussed growth in its relation to autocatalysis. In a recent paper I have compared the equations of slowly and rapidly growing apricot shoots. In each case the rate was proportional to a function of the final length of the shoot. The shoots which had a greater final length at the end of the season grew more rapidly from the start than their shorter neighbors, though the growing periods of the two samples were the same. The particular point of interest lay in the fact that the equations representing the growth rates had the same value for the constant of the reaction, differing only in the value of the constant expressing the final length of the shoots.

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[1] Paper No. 84 from the University of California Graduate School of Tropical Agriculture and Citrus Experiment Station.

[2] Robertson, T. B., *Arch. Entwicklungsmech. d. Org.*, 37: 497–508. 1913.

The present paper attempts to supplement this work by investigating the growth of organisms which reached approximately mature size after being subjected to conditions which suppressed growth in early life.

In the former case the difference between the two lots was in their final size; in the present case the difference between the two lots was in the time required to make equivalent body weight.

A. THE RATE OF GROWTH OF RATS ON ADEQUATE DIETS

The growth of the white rat has been so completely studied by many investigators that no extended discussion of the subject is required.

The rate of growth of rats varies slightly in different lots, but in general it follows the course of a differential equation. In later paragraphs I shall show that the equations used are those which express an autocatalytic reaction. The rate at which each sex grows is quite characteristic. The females grow relatively faster in early life than the males, come sooner to maturity, and weigh less at maturity than the males.

The growth of a white rat in the first year comprises two cycles. The first cycle, covering approximately 150 days, consists of a rapid increase in the weight and size of the body. The second cycle, covering the remaining 200 days, consists of a thickening of the body and a deposition of fat. The growth of rats in each of these cycles may be expressed by the equation

$$\log \frac{x}{a-x} = K(t-t_1),$$

in which x represents the weight of the animals at time t, a represents their weight at the end of the cycle, t_1 is the time at which the weight, x, is one half a, and K is a constant.

Although the quantitative relationships of this growth rate have been ably discussed by Hatai,[3] it will be shown subsequently that there are numerous reasons for using the above-mentioned formulas for computing growth. The computation of these and other growth rates studied in this paper have been made with the aid of tables published by Robertson.[4]

Table I contains data on the growth of white rats in the first year of life. The data for the rats were taken from Donaldson's tables 63 and 64.

The equations for the growth of the animals are as follows:

Males, first cycle, $\log \frac{x}{228-x} = .0187\ (t-73)$

Males, second cycle, $\log \frac{x-220}{280-x} = .0123\ (t-213)$

Females, first cycle, $\log \frac{x}{170-x} = .0211\ (t-61)$

Females, second cycle, $\log \frac{x-170}{226-x} = .0086\ (t-191)$.

It will be noticed that the calculation of the second cycle involves a change of the axes of the coordinates so that the new point of origin is near the point at which the first cycle of growth ended. The first cycle of growth in the female appears to terminate somewhat earlier than that in the male and the value of K, the constant, was greater in the growth curve of the female. These relations agree with the repeated observation that in early life the female grows more rapidly than the male. In the second cycle the female grows less rapidly than the male.

The close agreement between the observed and the cal-

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[3] In Donaldson, *loc. cit.*

[4] Robertson, T. B., Univ. Calif. Publ. Physiol., 4: 211–228. 1915.

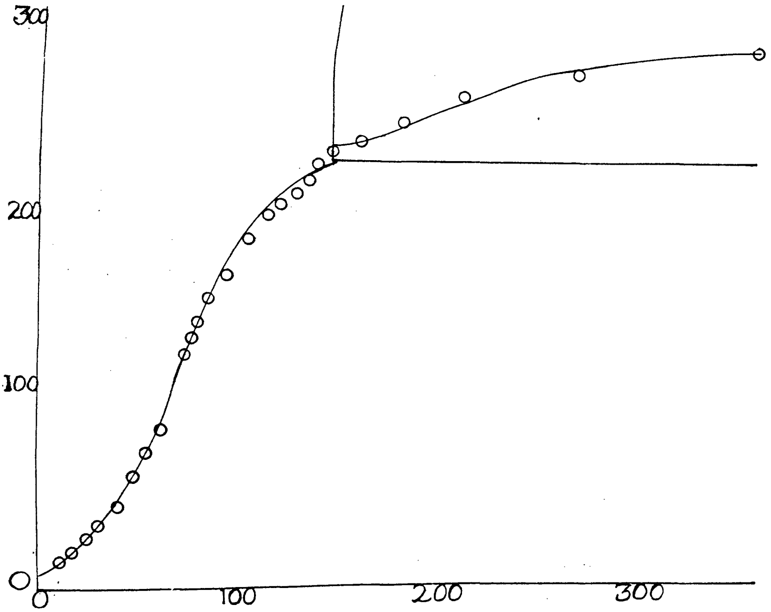

FIG. 1. Curve of growth for male white rat. . . . . , observed weight; ——, calculated weight. The weight for days 0–150 was calculated from $\log [x/(228-x)] = .0187\,(t-73)$. The weight for days 150–365 was calculated from $\log [(x-220)/(280-x)] = .0123\,(t-213)$.

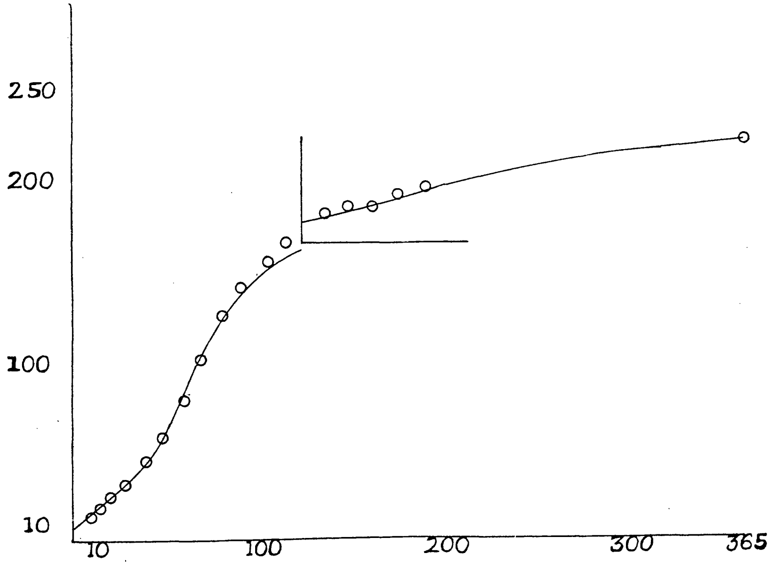

FIG. 2. Curve of growth for female white rat. . . . , observed weight; ——, calculated weight. The weight for days 0–124 was calculated from $\log [x/(170-x)] = .0211\,(t-61)$. The weight for days 124–365 was calculated from $\log [(x-166)/(226-x)] = .0086\,(t-191)$.

culated weights of the animals is shown by Table I and by Figs. 1 and 2.

B. The Growth of Rats Recovering from an Initial Period of Suppression

The published work of Osborne and Mendel contains very convincing evidence that the white rat possesses an inherent capacity for growth and that this capacity to grow survives long periods of suppression due to inadequate nutrition. Rats whose growth had been suppressed for over a year made prompt response and quickly reached mature size when the inhibiting factors were removed.

TABLE I

Growth of Albino Rats during their First Year [5]

Age (Days)	Males Weight		Age (Days)	Females (Unmated) Weight	
	Observed (Grams)	Calculated (Grams)		Observed (Grams)	Calculated (Grams)
First cycle			First cycle		
11	13	15	11	13	14
15	17	17	15	18	16
21	21	22	21	23	21
31	32	32	29	31	30
40	42	44	40	44	45
49	57	60	49	58	61
61	82	85	61	78	85
70	107	107	70	100	103
79	128	129	82	125	125
85	144	143	92	140	139
97	160	168	107	155	154
107	177	185	117	167	159
117	191	198	124	171	162
131	203	211	Second cycle		
143	218	217	124	171	179
150	225	220	131	179	180
Second cycle			138	182	182
150	225	229	143	183	183
157	227	230	150	185	184
164	231	232	164	185	188
171	236	234	178	192	192
178	239	236	192	196	196
185	240	239	365	226	224
216	253	251			
256	265	266			
365	279	279			

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[5] Data from tables 3 and 64 in: Donaldson, H. H. "The Rat." Philadelphia, 1915.

A second feature of their results, which is no less noteworthy than the first, is the rapidity of growth after adequate diets were given. They show that the gains made by the rats whose growth had been previously suppressed were made in much less time than would be required for a rat on adequate diet to make the same gain in weight.[6] This inquiry is concerned only with certain characteristics of the rate of growth following the initial period of suppression and will not attempt any discussion of the nutritional aspects of the problem. The data discussed have been drawn from the work of Osborne and Mendel. It has not been possible to obtain records of enough individuals to give a statistically reliable average, yet the records employed are fortunately free from extreme fluctuations and are satisfactory as far as individual records can go.[7]

The first case to be discussed is that of a male rat (No. 1012) which at age 370 days had reached a body weight of 127 grams, having been fed alternately "gelatin food" and "milk food."[8] On the 368th day the ration was permanently changed to "milk food plus mixed food." This change in diet was promptly followed by rapid growth and the attainment of mature weight about 180 days later. It is evident from Osborne and Mendel's chart that the curve of "resumed growth" was steeper than the normal curve of growth. This difference is especially well marked during that portion of the time in which there is an actual increase in body size and less well marked during the time in which its increase is due to the formation and deposition of fat.

A quantitative study of the resumed growth of this animal shows the existence of two distinct cycles, each of which is expressed by an equation of the type already discussed. From the time at which an adequate diet was supplied, until about the 432d day, the growth is expressed by the equation

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[6] Osborne, T. B., and Mendel, L. B., *Amer. Jour. Physiol.*, 40 : 16–20, 1916.

[7] The writer is greatly indebted to Dr. Osborne and Professor Mendel not only for their kindness in furnishing data, but for their criticism of this manuscript.

[8] Osborne, T. B., and Mendel, L. B., *Jour. Biol. Chem.*, 18 : 95–107, 1914, Chart V.

$$\log \frac{x}{220 - x} = .0193\ (t - 363).$$

This indicates a cycle of growth which was completed at a body weight of 220 g. and which overlapped slightly

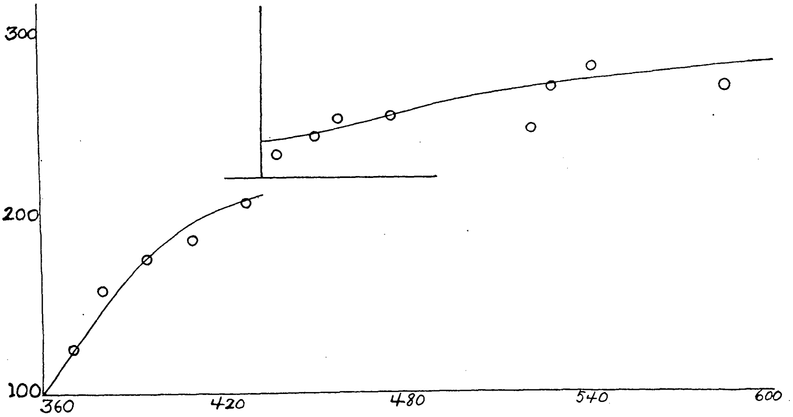

FIG. 3. Curve of growth of a male white rat following a suppression of 370 days. . . . . , observed weight; ——, calculated weight. The weight for days 360–432 was calculated from $\log [x/(220-x)] = .0193\ (t-363)$. The weight for days 433–600 was calculated from $\log [(x-220)/(288-x)] = .0091\ (t-475)$.

the second cycle of growth which was completed when a body weight of 288 g. had been attained. The equation representing the second cycle of growth is

$$\log \frac{x - 220}{288 - x} = .0091\ (t - 475).$$

The second cycle may be represented by a curve having ordinate and abscissa axes originating at $y = 220$ and $x = 432$. The values are shown in Fig. 3. The agreement between calculated and observed values is as good as could be expected with only one animal in the sample.

The next case to be noted is that of a male rat (No. 2161) which was stunted by a diet of inadequate protein from age 38 days to age 248 days.[9] During this

[9] Osborne, T. B., and Mendel, L. B., *Jour. Biol. Chem.*, 23 : 439–454, 1915.

period the increase in body weight was from 53 to 73 g. 220 days after an adequate diet had been begun the rat had grown to a weight of 300 g. The first cycle came to an end at the 368th day, when a weight of 230 g. had been reached, and is expressed by the equation

$$\log \frac{x}{236 - x} = .0180\,(t - 285).$$

The second cycle of growth is represented by the equation

$$\log \frac{x - 225}{305 - x} = .0150\,(t - 408).$$

For a graphic representation of these values see Fig. 4.

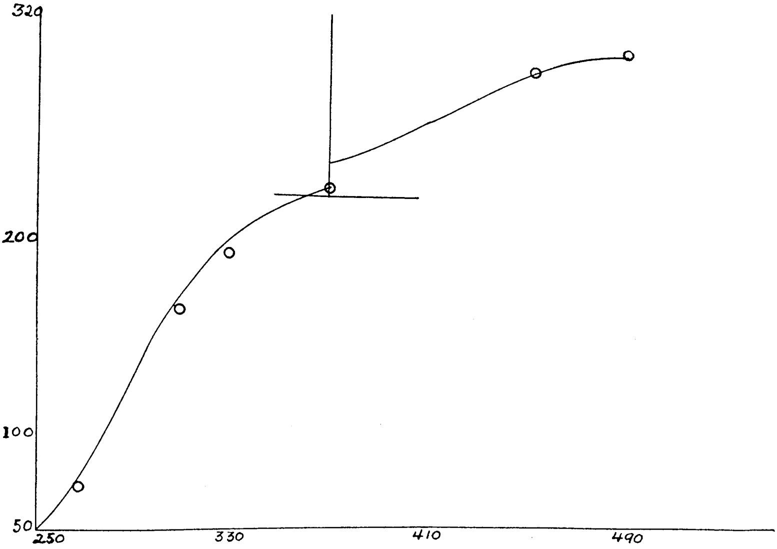

FIG. 4. Curve of growth of a male white rat following a suppression of 248 days. . . . . , observed weight; ——, calculated weight. The weight for days 248–368 was calculated from $\log [x/(236-x)] = .0180\,(t-285)$. The weight for days 368–488 was calculated from $\log [(x-225)/(305-x)] = .0150\,(t-408)$.

The third case studied was that of a female white rat (No. 2033) whose growth had been retarded by limiting the daily quantity of food.[10] Although the weight of this animal was held below 60 g. for the remarkably long period of 510 days, it had not lost the capacity for growth.

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[10] Osborne, T. B., and Mendel, L. B., *Jour. Biol. Chem.*, 23 : 439–454, 1915. Also *Amer. Jour. Physiol.*, 40 : 16–20, 1916.

After 135 days on an adequate diet it weighed 222 g.

The equations for the first and second cycles of growth of this animal are

$$\log \frac{x}{175 - x} = .0260\ (t - 519)$$

and

$$\log \frac{x - 170}{230 - x} = .0231\ (t - 610).$$

For a graphic representation of these values see Fig. 5.

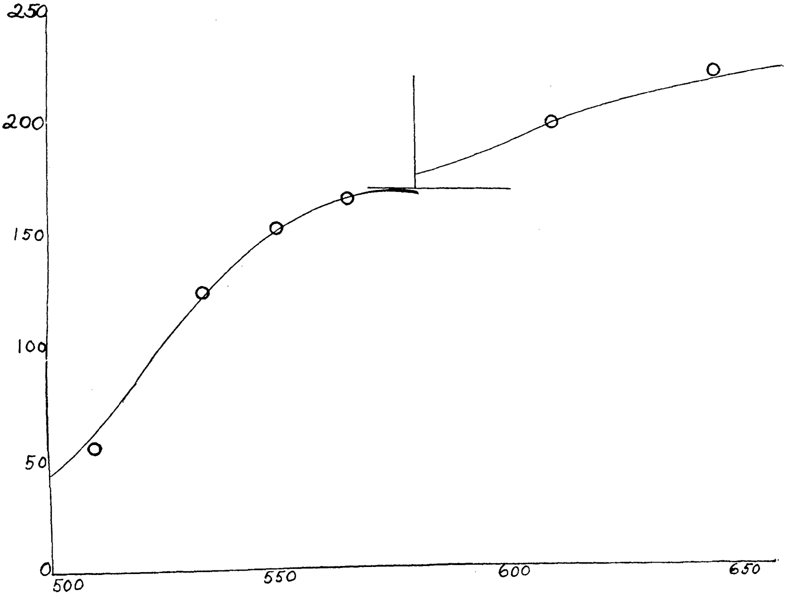

FIG. 5. Curve of growth of a female white rat following a suppression of 500 days. . . . . , observed weight; ———, calculated weight. The weight for days 500–580 was calculated from log $[x/(175—x)] = .0260\ (t—519)$. The weight for days 580–660 was calculated from log $[(x—170)/(230—x)] = .0231\ (t—610)$.

The constants of the different equations are grouped for convenience in Table II. From them it appears that male rats fed on adequate diet reached a weight of 280 g. at the end of their first year, and the female rats a weight of 230 g. in the same time. The females grow relatively faster in the first cycle than the males and in harmony with this property the values of K (the constant of the reaction) in the first cycles were greater than those of the males. The values of K in the second cycles were less than those in the first cycles. In the case of males on adequate diet the value of K in the second cycle is about 66 per cent. of its value in the first, but in the females the value in the second cycle is only 33 per cent. of that in the first cycle.

The values of the constants are somewhat different in the cases of rats subjected to an initial period of suppression. Rat No. 1012 reached approximately the same body weight as a male rat fed continuously on adequate diet. Its weight was 127 g. when full feeding began on the 368th day; the gain was, therefore, 153 g. in 212 days. The male rats on adequate diet weighed 127 g. at the 77th day; their gain of 153 g. was, therefore, made in 286 days. The animal recovering from initial suppression, therefore, required considerably less time to make an increase from 127 g. to 280 g., than adequately fed animals required to reach the same stage of development.

The case of No. 2033 (female) has special interest because of the remarkably long period of stunting. The period of suppression started on the 39th day when the rat weighed 53 g. and ended on the 510th day when it weighed 57 g. The animal attained a weight of 222 g. in 135 days, following the resumption of full feeding. A female rat on adequate diet from the time of weaning would require 295 days to increase from 57 g. to 222 g., or more than twice the time to make the same gain. Other records of the time required by stunted and by adequately fed animals to attain a given weight are given by Osborne and Mendel[11] and in all cases the time was greatly reduced in the case of animals recovering from stunting. These authors likewise pointed out the broad biological significance of this faster growth rate. This question of rate is one of extreme interest in connection with the dynamical aspects of growth

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[11] Osborne, T. B., and Mendel, L. B., *Amer. Jour. Physiol.*, 40: 16–20, 1916.

TABLE II

COMPARISON OF CONSTANTS

	First Cycle		Second Cycle		Duration of both Cycles
	a	*K*	*a*	*K*	
On adequate diet. Male	228	.0187	280	.0123	365 days
On adequate diet. Female	175	.0234	230	.0076	365 days
On restricted diets:					
No. 1012. Male	220	.0193	288	.0091	263 days
No. 2161. Male	236	.0180	300	.0150	286 days
No. 2033. Female	175	.0260	230	.0231	162 days

C. RATES OF GROWTH AS COMPUTED FROM VALUES OF dx/dt

It is unnecessary to dwell upon the prime importance of the study of rates in physiological investigations. We are concerned not only with what the organism is, but how it came to be what it is. As soon as we begin to study the problem of development, we encounter the question of rates. No better means of studying the rate of change in a system has yet been found than the differential calculus.

The differential equation representing the rate of autocatalysis is

$$\frac{dx}{dt} = kx\,(a - x).$$

a, x and t represent the same values as before, but $k = K/a$. We may proceed, therefore, to examine the derivatives of the equations used above to express the sizes of the animals at various time intervals. The values obtained for the growth of males and females are shown in Figs. 6 and 7 in comparison with the observed weekly increases of the animals which have been studied. The computed values were obtained from the tables published by Robertson[12] which give the values of $(1/Ka) \cdot (dx/dt)$ for corresponding values of $K(t - t_1)$.

The rate of growth of male rats on adequate diet was computed for each cycle from the figures in Table I. The rates for each cycle are shown in Fig. 6. The growth rate at birth had an appreciable value, as one might expect.

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[12] Robertson, T. B., Univ. Calif. Publ. Physiol., 4 : 211–228, 1915.

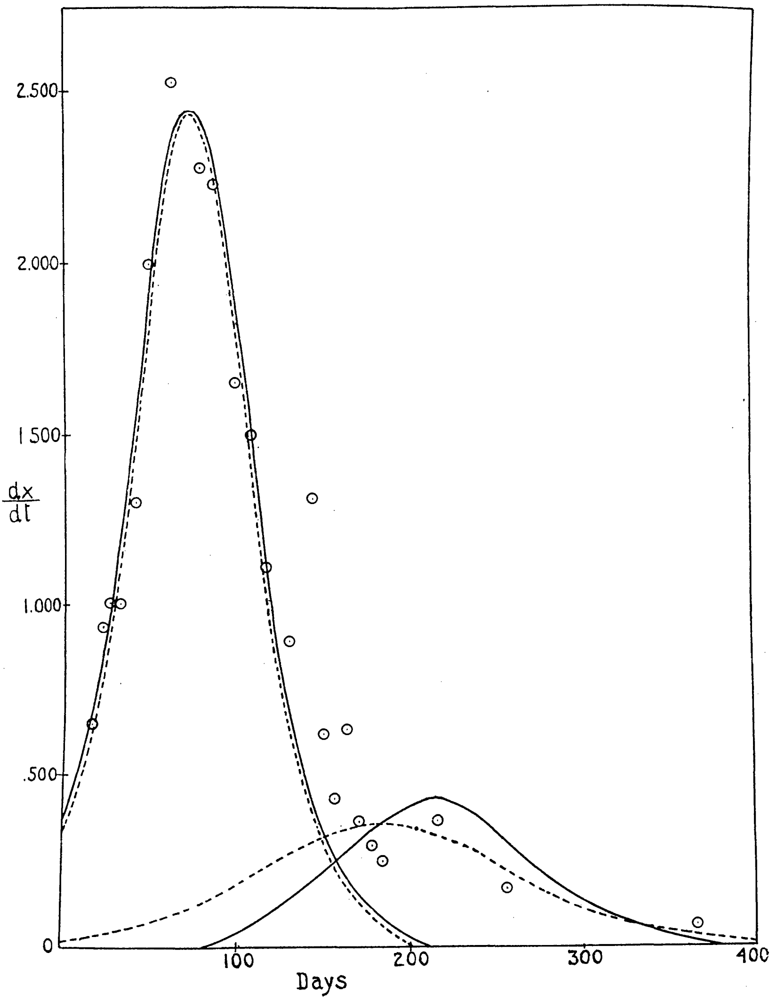

FIG. 6. Growth rates of male white rats. . . . . , observed increments of rats on adequate diet; ——, calculated values of *dx/dt* for rats on adequate diets; —— calculated values of *dx/dt* for rat recovering from a suppression of 370 days.

From birth to the 73d day the rate rose rapidly to its maximum, then fell to zero value of *dx/dt* at about the 215th day.

Before the first growth cycle was ended the second cycle had begun. The computed values show that this second cycle began about the 80th day of postnatal life, reached a maximum about the 213th day and ceased shortly before the 400th day. Since the value of $kx(a-x)$ approaches zero when x is very small and again when x is nearly

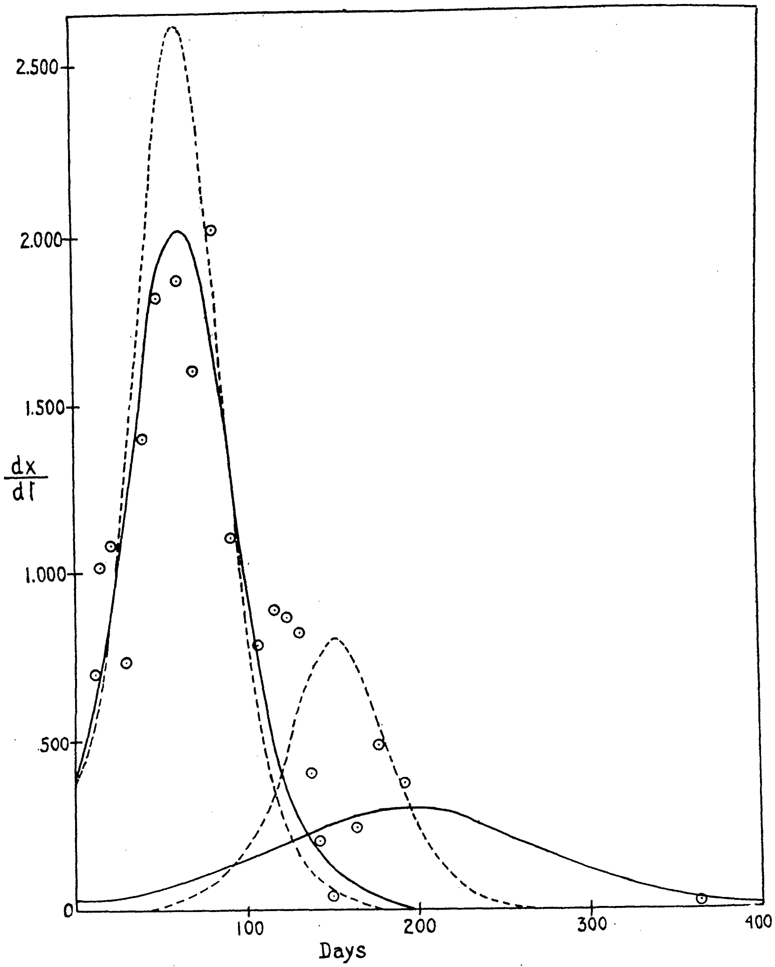

FIG. 7. Growth rates of female white rats. . . . . , observed increments of rats on adequate diet; ——, calculated values of dx/dt for rats on adequate diet; —— calculated values of dx/dt for rat recovering from a suppression of 500 days.

as large as a, it is possible to trace the curve in both directions until it reaches zero values of dx/dt. The actual values of dx/dt in the second cycle are much smaller than those in the first cycle.

Attention must be drawn to the way in which these two curves overlap. It will be noted that the second cycle of growth began shortly after the rate of the first cycle began to decline and that the first cycle continued to about the time of maximum rate in the second cycle. The true curve of the growth rate of these animals is, therefore, the arithmetical sum of the values of dx/dt for the various values of t. This is shown in Fig. 6 and agrees very well with the observed weekly increments.

The curves in Fig. 6 were obtained by plotting dx/dt as ordinate and t as abscissa.

If we let $dx/dt = z$, we may write

$$z - kx(a - x),$$

which when differentiated becomes

$$\frac{dz}{dx} = ak - 2kx.$$

If the right-hand member of this equation be equated to zero it will give the values of x for which z is either maximum or minimum.

Let $ak - 2kx = 0$; then

$$2kx = ak,$$
$$x = a/2.$$

Therefore the rate, z, is either maximum or minimum when $x = a/2$. To find whether z is maximum or minimum it is only necessary to get the second differential of the above equation

$$\frac{d^2z}{dx^2} = -2k.$$

Since this quantity has a negative sign z ($= dx/dt$) is a maximum when $x = a/2$. In other words the rate of growth is a maximum when the cycle has reached a stage at which the weight of the animal is half the weight it attains at the end of that cycle. When $x < (a/2)$ the curve rises and when $x > (a/2)$ the curve falls.

The rate of growth of an animal recovering from an initial period of suppression may be studied in comparison with that of a rat on adequate diet. Take the case of rat No. 1012 (male). The computed values of dx/dt have been plotted in Fig. 6. The time at which dx/dt was a maximum in the first cycle was made to coincide with the maximum for the first cycle of the rats on adequate diet. This arrangement was adopted to facilitate comparison.

The curve for the first cycle as plotted in Fig. 6 is a very fair duplicate of the curve for the same cycle of growth for the rats on adequate diets. There is more difference in the case of the second cycle. The curve for rat No. 1012 has a maximum which is lower and occurs somewhat nearer the dx/dt axis than that of the other class of animals. In other words, the increased weight due to formation of fat in this animal began relatively earlier than in animals on adequate diets. In the main, however, there are no striking differences between the relative growth rates in the two cases, except that their maxima are nearer together.

The same sort of computations have been made for the growth of female rats and they are shown graphically in Fig. 7. An extended discussion of them is unnecessary, as it would be in many respects a mere repetition of what has been said. A comparison of the curves of female rats on adequate diet with those of rat No. 2033 shows (*a*) that the rate of resumed growth was faster in the second cycle, (*b*) that the second cycle was of shorter duration, and (*c*) that the maximum of the second cycle lay closer to that of the first cycle than in the case of rats on adequate diet.

In view of the fact that rats recovering from initial suppression reach mature weight more quickly than animals fed on adequate diets, it is somewhat surprising to find such a close similarity in the values of dx/dt for the same time intervals. One might expect that the curves for the recovering animals should be higher and steeper.

I believe that the reason for the quicker growth in the recovering animals lies, not in a faster growth rate in the cycle, but in the shorter time between the maxima of the two cycles. In other words, the final weight is reached more quickly because the second cycle of growth commences relatively earlier and is added to the first cycle. Unfortunately, the weights of recovering animals were not taken at sufficiently frequent intervals to afford data upon the actual rates of growth in this class.

If we assume that growth is the result of a catalyst acting upon a substrate, it seems that we have a key to the explanation of what is observed. The catalyst of the first cycle was produced in the pre-natal stages. Although there was no appropriate substrate available in the starved animals, the catalyst did not disappear. When an appropriate substrate was given, this catalyst acted upon it, producing a cycle of growth essentially equivalent to that shown by animals fed on adequate diets. This may mean that the catalyst persisted unimpaired until it was destroyed in the course of the reaction. The catalyst responsible for the second cycle likewise appeared and induced the formation of fat. If the second catalyst is in some way dependent upon a time factor for its formation (or activation) it is plain that it should show its activity relatively earlier in the case of animals recovering from a long period of initial suppression, because of a *quasi* cumulative age effect. The effect of this would be what we have seen to happen, viz., a crowding of the cycles nearer together.

The writer is fully aware of the hazards encountered in attempting to represent so complex a reaction as growth by a simple formula. The phenomena of growth appear, however, to be coordinated into a single self-consistent process, in which many chemical and physical factors are combined. The possibility of expressing growth by a simple formula showing that an increase in mass is definitely related with a function of time ought to lead to considerations of a fundamental nature.

D. SUMMARY

1. The growth of white rats during the first year shows two cycles, and each cycle follows the course of an autocatalytic reaction. The first cycle covers the period in which the skeleton rapidly increases in size; the second covers the period in which there is a production and deposition of fat.

2. The equations for the growth of the two sexes differ in their constants, but each expresses the course of an autocatalytic reaction.

3. The earlier period of stunting did not prevent the animals from attaining the full weight characteristic of their sex after having an adequate diet. An equivalent gain in weight was made more quickly in the animals recovering from suppression than in animals on adequate diet.

In other words the animals grew somewhat more rapidly during their period of recovery.

4. The growth of white rats recovering from a long period of suppression follows the curve of autocatalysis, though a portion of the first cycle has been run during the long period of suppression.

5. The differential equations expressing the growth rates show that the two cycles overlap to some extent. The sums of the overlapping values approximate closely the observed increments. The second cycle of growth of rats recovering from starvation began and reached its maximum relatively earlier than in the case of rats on adequate diet.

6. There is evidence for the idea that each cycle of growth in this case had its specific catalyst and that the potential activity of the catalyst was not impaired by long periods of inadequate nutrition.